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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/679,670	PASZTY ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 63-66 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 63-66 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 06 October 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 20040621.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities: SEQ ID NOs: 4 and 6 do not agree with Fig. 2A-C or with SEQ ID NO: 3, which would not encode SEQ ID NO: 4 or 6. SEQ ID NO: 4 and 6 are missing three consecutive amino acids, GlyAlaArg, corresponding to amino acids 173-175 (GAR) from Fig. 2B, and amino acids 196-198 in Fig. 2C. Claims reciting SEQ ID NO: 4 were examined using the sequence disclosed in Fig. 2B, rather than SEQ ID NO: 4.

Appropriate correction is required.

Claim Rejections - 35 USC § 101 & 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-66 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. In the absence of a specific and substantial asserted utility, credibility could not be assessed.

The claims are directed to methods of treating a generic and unspecified disease, condition or disorder in a patient with: 1) a compound that selectively binds to a polypeptide, or fragment of such a polypeptide, comprising the amino acid sequence of SEQ ID NO: 2 or 4, the human or mouse cloaked-2 proteins, respectively, or a natural variant of such a polypeptide, as in claim 63; 2) a polypeptide comprising SEQ ID NO: 2 or 4 or encoded by a nucleic acid molecule encoding SEQ ID NO: 2 or 4, such as a nucleic acid comprising SEQ ID NO: 1 or 3 respectively, or a nucleic acid molecule that encodes a polypeptide having an unspecified activity of the polypeptide of SEQ ID NO: 2 or 4 that hybridizes to the complement of a nucleotide sequence encoding SEQ ID NO: 2 or 4, as in claim 64, parts (a)-(c) and claim 65; 3) a polypeptide encoded by the complement of the nucleic acid sequence indicated in (2), as in claim 64, part (d) ; 4) a nucleic acid molecule that encodes a polypeptide indicated in (2), as in claim 66, parts (a)-(c); or 5) a nucleotide sequence complementary to the nucleotide sequence indicated in (4), e.g. an antisense or ribozyme, as in claim 66, part (d).

The specification discloses, based only on structural features, that the Cloaked-2 protein is distantly related to proteins of the cystine-knot growth factor structural super-family. The specification provides no evidence identifying a specific function for the Cloaked-2 protein at any level. It does not disclose any biochemical function, other than the vague assertion that it would bind an unidentified receptor, presumably since other members of the super family, e.g. TGF-β, PDGF, NGF, bind receptors to initiate cellular processes. It does not disclose any

physiological function for Cloaked-2 either at the level of a cell, of a tissue, or an organism, nor a specific biochemical function for Cloaked-2, i.e. no receptor for the protein is identified. Beyond the disclosed nucleotide and predicted amino acid sequences, the specification presents information only on tissues which express Cloaked-2 mRNA, strongest in heart and kidney.

The specification asserts that the recited nucleic acid molecules, the polypeptides encoded thereby or antibodies may be used to treat a "nonexclusive list" of apparently unrelated diseases (pages 99-103). The assertion appears to be based on the unsubstantiated hypothesis that Cloaked-2 has hormonal or growth-factor activity, and on the expression pattern seen for Cloaked-2 mRNA expression. The specification does not disclose whether the goal for such treatment of the listed diseases should be the increase or augmentation of Cloaked-2 activity (claim 64, (a)-(c), claim 65 and claim 66, (a)-(c)) or its inhibition or decrease (claim 63, claim 66(d)). The specification does not identify any activity of Cloaked-2 whose excess or loss would correspond to any of the listed diseases or conditions. With respect to claim 64, part (d), the specification does not describe any polypeptide encoded by the complement of a nucleotide sequence encoding a Cloaked-2 protein or related protein, or what disease or condition would be treated with such an unknown polypeptide. Such a complement, if it encoded any polypeptide at all, would not encode a polypeptide structurally related to cloaked-2. Consequently, the specification provides no basis that would lead one of skill in the art to reasonably accept that the specification disclosed a method for treatment of any of the diseases or conditions listed in a readily available form. Consequently, it would be left to one of skill in the art to reasonably confirm or refute these asserted uses, and to determine which, if any, the recited binding agents, polypeptides or nucleic acid molecules could be used as a means for treatment of any of the

listed diseases or conditions. The disclosure of highly speculative, general and nebulous uses as here does not meet the requirement for a specific and substantial utility. *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967)

In addition, Brunkow et al. (Am. J. Hum. Genet. 68: 577-589, Feb. 2001) discloses a mammalian gene called *SOST*, which in human and mouse encodes a protein identical to instant SEQ ID NO: 5 and 6, respectively, which are the precursor forms of SEQ ID NO; 2 and 4, respectively (see Fig. 6). As shown in Fig. 7 of Brunkow, SOST is expressed in bone and cartilage far more than in any other tissue. Loss of *SOST* function in humans leads to sclerosteosis, which is characterized by progressive skeletal bone growth, with normal osteoclast function and defective osteoblast function, and no endocrine abnormalities, (i.e. its not a hormone). Brunkow et al., US 6,395,511 discloses that BEER protein (a.k.a. SOST) binds to and inhibits the function specifically of BMP-5 and BMP-6, i.e. not a growth factor, but a growth factor inhibitor (see Abstract and claim 1). There is no evidence whether or not BEER/SOST/CLOAKED-2 binds a cellular receptor as suggested in the instant specification. It is significant that none of the diseases listed in the instant specification relate to bone or cartilage disorders or include sclerosteosis, and sclerosteosis is not characterized by any of the conditions listed in the specification. The Brunkow article was published after the date to which priority is being claimed, and the Brunkow patent issued after the instant application was filed, and most important the instant specification fails to disclose even a hint of what either Brunkow reference discloses concerning the activity and uses of the recited binding agents, polypeptides or nucleic acid. Consequently, this information cannot be used to supplement the deficiencies of the instant

specification, since the specification must set forth the uses and the utility requirement must be met by the application when at the time it is filed. *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967).

The Supreme Court has held that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. "[A] patent system must be related to the world of commerce rather than to the realm of philosophy." *Brenner v. Manson*, 148 USPQ 689, 696 (US 1966). The instant specification provides no more than suggestions of avenues of further characterization of Cloaked-2 and identification of potential diseases that might be treated with the nucleic acid, antisense or ribozymes to the nucleic acid, the polypeptide or agents that bind to the polypeptide, without reasonably assuring the public of any benefit derived therefrom in an immediately available form as required under §101. The specification does no more than suggest to one of skill in the art to go out and identify a disease in which cloaked-2 or the loss of cloaked-2 might play a role and then determine whether any of the recited products might be used to treat the disease or condition.

Claims 63-66 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 64 and 66 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with the claims, and;

Claims 63, 64 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 63, in part (c) is directed to a naturally occurring variant of SEQ ID NO: 2 or 4. As indicated below, it is unclear what level or type of variation is embraced by this part of the claim. Claims 64 and 66, in part (c) of each, are directed to a nucleic acid molecule which encodes a polypeptide having "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4" and that hybridizes under high or moderate stringency to the complement of a nucleotide sequence that encodes SEQ ID NO: 2 or 4. The specification enables how to make and provides an adequate written description for a nucleic acid molecule which encodes a polypeptide with "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4", wherein the nucleic acid molecule either comprises SEQ ID NO: 1 or SEQ ID NO: 3 or encodes SEQ ID NO: 2 or SEQ ID NO: 4. The specification neither enables how to make nor adequately describes any other nucleic acid molecule which encodes a polypeptide with "an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4."

Claim 64, part (d) is directed to a polypeptide encoded by the complement of a nucleotide sequence encoding a Cloaked-2 polypeptide. The specification does not teach any such polypeptide, nor identifies any characteristic of such a polypeptide whatsoever. Thus, the specification clearly fails to describe such a polypeptide or enable how to make it.

While the written description and enablement requirements are separate and generally separable requirements, the instant application fails to meet either requirement for essentially the

same reasons. The primary reason is that the specification fails to identify a single "activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4", whether biochemical, biological or physiological. Indeed, it cannot be determined from the specification whether the polypeptide of SEQ ID NO: 2 even has an activity of the polypeptide of SEQ ID NO: 4, and *vice versa*. For example, the specification provides no evidence that the human Cloaked-2 would complement the loss of Cloaked-2 function in a mouse, or that the human Cloaked-2 would bind the same mouse receptor as murine Cloaked-2, if one assumes that Cloaked-2 acts by binding a cellular receptor as do other characterized members of the cystine-knot protein super family. The specification also fails to provide a single method or assay for determining whether a given nucleic acid molecule meeting the structural limitations of the claims, e.g. hybridization, encodes a polypeptide actually having an activity of the polypeptide as set forth in SEQ ID NO: 2 or SEQ ID NO: 4. While a polypeptide of SEQ ID NO: 2 or 4 may reasonably be assumed to have an activity characteristic of itself, whatever that may be, any specific variant of these polypeptides cannot be assumed to have such an activity given the dearth of descriptive and enabling support in the specification as to what that activity is or how to determine it. For example, if one of skill in the art were provided a nucleic acid molecule encoding a polypeptide differing from SEQ ID NO: 2 by a single amino acid, the specification does not provide any descriptive support that would allow one to envision whether the polypeptide would have the requisite activity, nor does it describe a method enabling one to determine by experimentation whether the encoded polypeptide had the requisite activity, i.e. one would be unable to determine whether the nucleic acid molecule was embraced by the claims, whether it was a naturally occurring variant or a man-made variant. One would be unable to determine whether the change would result in a loss

of polypeptide function, an alteration of polypeptide function, e.g. a dominant-negative mutation, or would be a neutral or silent change.

With respect to naturally occurring sequence variations, e.g. as in claim 63 or embraced by claims 64 and 66, the specification provides the sequence for a single such variant, i.e. SEQ ID NO: 2 for SEQ ID NO: 4 and *vice versa*, nor does it provide objective evidence that such other variants even exist. If one were provided a nucleic acid molecule differing from SEQ ID NO: 1 or 3 or polypeptide differing from SEQ ID NO: 2 or 4 by even so little as a single residue, the specification provides no information that would allow one to determine whether the sequence arose in nature or was a sequence created by man which has no counterpart in nature. The specification provides neither a description nor a method for determining whether the variant is functional or non-functional or has an activity of the polypeptide of SEQ ID NO: 2 or 4, even if the variant were natural.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA or protein solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA or protein with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that

material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

In terms of the structural requirements of the nucleic acid molecules, the only difference between the cases reviewed by the court and Board, and the instant case, is that in addition to recitation of a desired protein activity, claims 64 and 66 recite an arbitrary structural relationship between the claimed nucleic acid sequence and the single disclosed species of nucleotide sequence and amino acid sequence, respectively, based upon hybridization of nucleic acid. Hybridization of two nucleic acids under high stringency conditions requires only that the two nucleic acids share between 25 and 50 nucleotides in common. See Kennell, Progr. Nucleic Acid Res. Mol. Biol. 11: 259-301, 1971 at the paragraph bridging pages 260-261. Such a sequence encodes only 8-16 amino acids. Consequently the claims embrace polypeptides that could share as few as 8-16 contiguous amino acids in common out of the 190 or 188 amino acids of SEQ ID NO: 2 or 4, respectively. Conversely, a nucleotide sequence that differs in every wobble base from SEQ ID NO: 1, for example, would encode SEQ ID NO: 2, but would not detectably hybridize to SEQ ID NO: 1 under any conditions. Thus, the recited structural relationship is arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at the nucleotide level; and the

specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to SEQ ID NO: 1 or 3 or that encodes a polypeptide that is not 100% identical to SEQ ID NO: 2 or 4.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that hybridize to a reference nucleotide sequence under a given set of conditions and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences, to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, the mouse and human Claoked-2 polypeptides are approximately 90% identical, and their cDNA would hybridize under moderate or high stringency since they share a stretch of about 70 contiguous nucleotides (beginning at nucleotide 475 of SEQ ID NO: 3). If one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a polypeptide with Cloaked-2 function than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence - even were the Cloaked-2 function known. Nor would he be able to say whether the sequence existed in nature.

The specification does not provide any information on what amino acid residues are necessary and sufficient for the undisclosed activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be

permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there were no other examples of a functional Cloaked-2 protein known that have structural homology with SEQ ID NO: 2 or 4, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. The comparison of SEQ ID NO: 2 to 4 is no help since it has not been disclosed whether these proteins share an activity, e.g. binding to a specific human receptor. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the instant Cloaked-2 protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a protein with an activity of SEQ ID NO: 2 or 4 with an amino acid sequence differing from SEQ ID NO: 2 or 4 since the amino acid sequence of such polypeptides could not be predicted - even were the activity known.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only one putative functional amino acid sequences, SEQ ID NO: 2 or 4, for a polypeptide having the necessary activity, and provides no guidance on determining which polypeptide variants of SEQ ID NO: 2 or 4 which would have an activity of SEQ ID NO: 2 or 4.

To put the situation in perspective, the number of possible amino acid sequences of 190 amino acids in length is 20^{190} (approx. 10^{247}). The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following expansion formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + ... + X^{n-1}L(L-1)(L-2)...(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)...(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The n^{th} term of the expansion can be rewritten as:

$$X^n \cdot {}^{L!}/_{(L-n)!n!}$$

For a 190 amino acid sequence that is at least 90% identical to a reference sequence of 190 amino acids, e.g. SEQ ID NO: 2, the number of possible sequences having 18 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 7×10^{47}, whereas the number of possible sequences having 19 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1×10^{50}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. Also, as the number of permitted substitutions increases the number of possible variant sequences increases geometrically. In a genus of polypeptides that are at least 90% identical to a reference, nearly all will be exactly 90% identical. As indicated above, the claim permit the polypeptides to share as little 8-16 amino acids in common with SEQ ID NO: 2 or 4 based upon the hybridization limitation, or less than 10% sequence identity. There would be approximately 2×10^{245} potential amino acid sequences differing from SEQ ID NO: 2 by 174 substitutions. While limiting the scope of potential sequences to those that are at least 90% identical to a reference, for example,

greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. The mass of the Earth is about 6×10^{24} kg. One microgram of 570 nucleotide dsDNA molecules (required to encode 190 amino acids) contains approximately 1.5×10^{12} DNA molecules. If it were possible to convert the mass of the Earth (6×10^{30} μg) into such DNA molecules, one would obtain about 10^{42} DNA molecules. Thus, one would require about 10,000,000 times the mass of the Earth of DNA to produce just one nucleic acid molecule encoding each of the 10^{50} possible amino acid sequences differing from SEQ ID NO: 2 or 4 by substitution of 10% of their amino acids.

Therefore, inclusion of the recited structural relationships in the claims do not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.* Thus, even were an activity of human or murine Cloaked-2 disclosed, the instant specification would be inadequate to describe and enable how to make the nucleic acid molecules as broadly as they are claimed here.

Claims 63, 64 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 63 recites "naturally occurring variant of" an amino acid sequence of SEQ ID NOs: 2 or 4 or a fragment of one of these. The metes and bounds of the "naturally occurring variant" are unclear. The amino acid sequences of SEQ ID NOs: 2 and 4 fall structurally within the cystine-knot growth factor structural super-family, which includes the TGB-β superfamily of proteins, which are presumed to have evolved from a common ancestral gene. Consequently, all

members of this family of proteins are naturally occurring variants of one another. However, when read in light of the specification, interpreting the claims so as to embrace all members of the cystine-knot growth factor structural super-family would be unreasonable. At the very least, the "variant" would embrace orthologs of the SEQ ID NO: 2 and 4, those homologs found in other species that are closest in structure and have the same physiological function. However, it is unclear which other members of the cystine-knot growth factor structural super-family superfamily are included or excluded by the claims when reasonably interpreted in light of the specification.

Claim 64 is directed to treatment with a polypeptide that is encoded by a nucleotide sequence. Parts (a) –(c) specify nucleotide sequences that encode SEQ ID NO: 2 or 4, or are encoded by a polynucleotide that would hybridize to the complement of these, e.g. a polynucleotide that would encode a sequence variant of SEQ ID NO: 2 or 3. Part (d) however specifies a polypeptide that encoded by nucleotide sequence that is complementary to a sequences recited in parts (a)-(c). It is not clear what, if any, polypeptide would be encoded by such a complement. It clearly would not encode SEQ ID NOs: 2 or 4 or a sequence variant of one of these because the complement of SEQ ID NO; 1, for example, is the non-coding strand. Thus, part (d) of the claim makes no sense, and should be deleted.

Claim 66 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are the elements required to express a polypeptide, presumably a cloaked-2 polypeptide, from the nucleotide sequences recited in parts (a)-(c) of the claim. The specification describes treatment with two types of nucleic acids. First, a nucleic acid that encodes a cloaked-2 polypeptide, and second, a

polynucleotide that inhibits expression form a cloaked-2 gene, such as an anti-sense oligonucleotide. Parts (a)-(c) correspond to the first of these, while part (d) corresponds to the latter. In for the nucleic acid to be operative for the expression of a cloaked polypeptide, the nucleic acid must include nucleotide sequences that mediate expression of the polypeptide from the nucleic acid molecule, a promoter and polyA signal for example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 63 and 66 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Brunkow et al. US 6,395,511, filed 11/24/99 claiming priority to 60/110,283 filed 11/27/98. The '283 provisional application discloses the coding sequence for the human BEER polypeptide and the human BEER polypeptide and vectors, but does not disclose the murine sequences, and

generally teaches the methods of using antibodies or anti-sense oligonucleotides to increase bone mineral content.

SEQ ID NO: 1 nucleotides 12-770 are identical to instant SEQ ID NO: 1, and encodes human BEER polypeptide, SEQ ID NO: 2, which is identical to instant SEQ ID NO: 5, and amino acids 24-213 of which are identical to instant SEQ ID NO: 2, i.e. it differs from instant SEQ ID NO: 2 insertion of 23 amino acids at the amino terminus. If the polypeptides of instant SEQ ID NO: 2 and 4 share an activity (which has not been disclosed in the instant specification), then the prior art polypeptide presumably has an activity of the polypeptide of instant SEQ ID NO: 4. Amino acids 24-213 differs from instant SEQ ID NO: 4 by 10 conservative substitutions, 8 non-conservative substitutions, and an insertion of 2 amino acids.

SEQ ID NO: 11, nucleotides 1-636 are identical to instant SEQ ID NO: 3, and encodes murine BEER polypeptide, SEQ ID NO: 12, which is identical to instant SEQ ID NO: 6, and where amino acids 24-211 are identical to instant SEQ ID NO: 4. If the polypeptides of instant SEQ ID NO: 2 and 4 share an activity (which has not been disclosed in the instant specification), then the prior art polypeptide presumably has an activity of the polypeptide of instant SEQ ID NO: 2. Amino acids 24-213 differs from instant SEQ ID NO: 2 by 10 conservative substitutions, 8 non-conservative substitutions, and an deletion of 2 amino acids.

Brunkow (col. 38-40) teaches methods of treating a variety of diseases and conditions characterized by loss of bone mineral content by administration to patients of anti-bodies that specifically bind the disclosed Beer proteins, as in instant claim 63, and ribozymes or anti-sense oligonucleotides directed against the Beer gene or mRNA or gene therapy vectors that express

such a ribozyme or anti-sense nucleic acid. Such anti-sense or ribozymes are nucleotide sequences complementary to Beer encoding mRNA, as in instant claim 66, part (d).

Brunkow does not disclose treatment of a medical condition with a Beer protein or nucleic acid encoding a Beer protein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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